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(54) Title: THE PROCESS FOR THE PREPARATION OF A STABLE FIXED DOSE PHARMACEUTICAL COMPOSITION OF ANTI INFECTIVE AGENT/AGENTS AND MICRO ORGANISMS AS ACTIVE INGREDIENTS

(57) Abstract

Micro organisms are useful in management of diseases including diarrhoea and gastro intestinal diseases like pseudomembranous colitis, megacolon etc. They are also useful in prevention of gastro intestinal disturbances and diseases caused by anti–infective agents like ampicillin, amoxycillin, cloxacillin, clauvanic acid, cefuroxime axetel, cephalixin, erythromycin etc. For prevention micro organisms are to be taken along with anti infective agents. When micro organisms are combined with anti–infective agents for ease of administration and improving compliance and therapeutic effect, the combination is not found to be stable at room temperature as micro organisms are sensitive to anti–infective agents and are destroyed by effect of anti–infective agent in composition. The present invention relates to the process of preparing a stable fixed dose composition of anti–infective agent with micro organism as active ingredient. The process includes preparation of various dosage forms for oral route like capsule, tablet and liquid formulation. The process comprises of providing an appropriate barrier by way of selected coating procedure to one of the active ingredients in such a way that micro organisms are not affected by anti–infective agents. This results in a stable composition. By using an appropriate coating technique composition is made to remain stable over a period of 3–36 months at ambient/room temperature. The ratio of micro organism to anti–infective agents in a composition can be 1:2 to 1:25 by weight. The ratio of 1:5 by weight is found to be optimal for the purpose. The amount of coating is dependent on the type of coating technique, dosage form i.e. capsule, tablet or liquid and desired self life. The micro organisms of the composition were found to be active after variable time period. They also provided therapeutic effect and eliminated gastro intestinal disturbances associated with anti–infective agents when evaluated in humans.

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DESCRIPTION

THE PROCESS FOR THE PREPARATION OF A STABLE FIXED DOSE PHARMACEUTICAL COMPOSITION OF ANTI INFECTIVE AGENT/AGENTS AND MICRO ORGANISMS AS ACTIVE INGREDIENTS.

The present invention relates to a process of manufacturing a formulation containing anti-infective agent(s) with viable organisms which are susceptible to anti-infective agents. Micro organisms are used to prevent adverse effects like diarrhoea caused by anti-infective agents.

The present invention is directed to manufacturing of a formulation where in anti-infective agents and susceptible viable organisms are combined in such a way so that micro organisms, through susceptible to anti-infective agent, remain viable for the self life of a formulation and/or till they are consumed. Susceptible organisms are usually combined with anti-infective agents to prevent or minimise adverse effects of anti-infective agents like diarrhoea, pseudomembranous colitis, mega colon, etc.

Organisms are classified as pathogens and commonsals. Pathogens are responsible for various infectious diseases and are not normally present in that part of the body. They are also known as infectious agents. Commonsals are normally present in various parts of body and perform useful functions. They provide vitamin K, B-12, Thiamine, Riboflavin etc. to body.[1] They inhibit the growth of pathogens by variety of mechanisms.[2] Anti-infective agents are used to treat/prevent infectious diseases. They kill organisms by various ways. However they are not always specific for pathogens and also kill commonsals.[2] Destruction or reduction in number of commonsals results in loss of function of commonsals and various effects of these are seen.[2,5] These effects are known as adverse effects or side effects of anti-infective therapy. Diarrhoea with or without super-infection is one of such effects seen with anti-infective therapy.[3,4,6] Diarrhoea is seen as an adverse reaction to many antibiotics. But they are most commonly seen with broad spectrum antibiotics. The incidence of diarrhoea also depends on level of absorption from G.I. tract. They are less frequent with those getting completely absorbed compared to incompletely absorbed. They also depend on amount of drug used. The antibiotics causing diarrhoea include clindamycin, ampicillin, amoxycillin, cephalosporins (e.g. cefuroxime axetil, cefixime, cepahlexin ceftriaxone), amoxycillin + clauvanic acid, ampicillin + salbcutam, fluoroquinolens and other combinations of broad spectrum antibiotics, e.g. amoxycillin + cloxacillin.[3,5,6,7,8,9,10,11,12,13,16,18] Diarrhoea can be benign and secondary to transient dysfunction of normal colonic flora due to anti-infective agents[6] or super-infection by pathogens like clostridium difficile following alteration of normal flora by anti-ineffective agents.[7,4,19,20] Management in such an event requires cessation of anti-infective therapy[3,7,4] and use of other therapies. Other therapies which can be used include different kind of anti-infective agents e.g. metronidazole, vancomycin,[3,13,8] teicoplanin and/or use of organisms like lactobacilli, biofidobacterium,

saccharomyies boulardili, streptococcus thermophilus, enterococcus facecium SF 68, L Casei GG etc.[14,15,16] These can be combined with whole bowel irrigation with good results.[17] Organisms used[9] eradicate or help in eradicating pathogens by variety of mechanisms which include production of hydrogen peroxide or inhibition or adherence of pathogens to intestinal cells. Anti-infective agents induced diarrhoea prolong treatment, increase cost of therapy by increased number of[1] drugs to be used,[2] days of hospitalisation and [3]consultations. Sometimes they create life threatening situation e.g. pseudememberous colitis,[4,13,20] toxic megacolon.

The organisms named above can be used to treat diarrhoea when it occurs. They can also be used to prevent diarrhoea.[14,16,18] Commercially available preparations include lactobacillus alone (Lactiflora, Lactobacil, Lactocap, Lactovit, Sporlac) or in combination with streptococcus (Lacticyn) or Sacchromyces (Laviest). To prevent diarrhoea organisms are given along with the anti-infective agents. This requires consumption of minimum two different drugs i.e. an anti-infective agent and an organism. This decreases compliance of a patient.

Attempts have been made to put organisms and anti-infective agents into one formulation. Some of these are commercially available. Lactobacillus is commonly used organism. Anti-infective agents used in the formulation include ampicillin, (e.g. Alcillin plus from Alpine), amoxicycillin (e.g. Alox plus from Alpine), ampicillin + cloxacillin (e.g. Amplus from Jagsonpal, Elclox plus from Elder, Penmix plus from Dee Pharma, Pen plus from Systopic, Poxin Plus from Alpine), amoxicycillin + cloxacillin (e.g. Bicidal plus from Kee Pharma, Diclox from Croford Pharma, Twinclox plus from Alpine). They all are simple admixture

of anti-infective agents and susceptible organisms. However, analysis of commercially available, as well as prepared by us revealed that organisms incorporated into formulation does not remain viable and did not perform any useful function for which they were to be used. Neither organisms nor their activity could be detected as early as 7 days after putting lactobacilli with various antibiotics like ampicillin, amoxycillin, amoxycillin + cloxacillin etc. or in commercially available preparation. Though 60 million spores are put into formulation, none of them could be grown or demonstrated viable on glucose yeast extract agar plate. It also failed to produce lactic acid as evaluated by consumption of NaOH.

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The objective of present invention is to combine susceptible organisms into a pharmaceutical composition containing anti-infective agents and keep them viable for the self life of the formulation or till it is consumed.

The further objective of present invention is to minimise side effects of anti-infective agents resulting from destruction/alteration of normal flora by providing viable organisms along with anti-infective agent(s).

The further objective of present invention is to provide a pharmaceutical composition which is effective after longer period of storage.

The further objective of this present invention is to increase compliance by reduction / elimination in side effects of anti-infective agents.

The further objective of the present invention is to improve compliance by providing two drugs in one pharmaceutical composition.

The further objective of present invention is to provide organism at a desired site.

The following specification particularly describes and ascertain the nature of this invention and manner in which it is to be performed.

The anti-infective agent and organisms are to be identified. Their dosage route of administration and dosage form is finalised.

The susceptible organism are combined into the formulation in such a way that organisms remain viable for the self life of a formulation inspite of being in contact with anti-infective agent. To protect susceptible organisms from effect of anti-infective agent a protective barrier is created around organisms or anti-infective agent, in such a way that anti-infective agent cannot have effect on organisms. This results in viable organisms in presence of anti-infective agent. The organism remain viable as long as the barrier is maintained. This is like applying paint or a film on a substance to prevent corrosion by isolating it from surroundings.

The protective barrier is selected depending on route of administration and dosage form of the pharmaceutical composition (anti-infective agent + organism)

The pharmaceutical composition so manufactured is evaluated for stability and efficacy.

The pharmaceutical composition so manufactured is evaluated at different test conditions of temperature and humidity (45°C, 37°C at 80% relative humidity and ambient temperature) for time interval extending upto 12 months.

The samples of formulation were taken for study at 3 weeks intervals. Samples were analysed for presence of organisms by quantitative and qualitative microbiological techniques. These values were found to be comparable with amount of organisms introduced into formulation.

The samples of formulation were also analysed for presence of anti-infective agent by quantitative estimation. The values of anti-infective agents forms were found to be comparable to those introduced into the formulation.

Thus findings indicate presence of organism and anti-infective agent in same amount when formulation was evaluated at different time interval after it was exposed to different environment.

The formulations so created were found to have improved therapeutic efficacy in term of reduction/elimination of antibiotic induced diarrhoea.

Usually ampicillin causes maximum diarrhoea amongst penicillin. The reported incidence is as high as 20% with ampicillins. In 40 patients when ampicillin + lactobacilli were given in a pharmaceutical composition prepared as described in this application, none of them developed diarrhoea and everybody could complete the full course of antibiotic therapy. The non development of diarrhoea suggests efficacy of new pharmaceutical composition prepared according to present invention.

1. Following are examples of formulations containing various anti-infective agents and susceptible organisms. However, it is not intended that the scope of this invention be limited by these examples.

Example I		Example II	
Ampicillin	250 mgm	Ampicillin	500 mgm
Lactobacillus	60 million	Lactobacillus	60 million

Example III	
Amoxycillin	250 mgm
Lactobacillus	60 million
Example IV	
Amoxycillin	500 mgm
Lactobacillus	60 million
Example V	
Cloxacillin	250 mgm
Lactobacillus	60 million
Example VI	
Cloxacillin	500 mgm
Lactobacillus	60 million
Example VII	
Ampicillin	250 mgm
Cloxacillin	250 mgm
Lactobacillus	60 million
Example VIII	
Ampicillin	125 mgm
Cloxacillin	125 mgm
Lactobacillus	30 million
Example IX	
Amoxycillin	250 mgm
Cloxacillin	250 mgm
Lactobacillus	60 million
Example X	
Amoxycillin	125 mgm
Cloxacillin	125 mgm
Lactobacillus	30 million
Example XI	
Ampicillin	1000 mgm
Sultamicin	500 mgm
Lactobacillus	60 million
Example XII	
Ampicillin	250 mgm
Probenecid	250 mgm
Lactobacillus	60 million
Example XIII	
Amoxycillin	250 mgm
Clavulanic acid	125 mgm
Lactobacillus	60 million
Example XIV	
Amoxycillin	500 mgm
Probenecid	500 mgm
Lactobacillus	60 million
Example XV	
Amoxycillin	250 mgm
Bromhexine	8 mgm
Lactobacillus	60 million
Example XVI	
Amoxycillin	250 mgm
Carbocisteine	150 mgm
Lactobacillus	60 million
Example XVII	
Amoxycillin	500 mgm
Bromhexine	8 mgm
Lactobacillus	60 million
Example XVIII	
Amoxycillin	500 mgm
Carbocisteine	150 mgm
Lactobacillus	60 million
Example XIX	
Cephalexin	250 mgm
Lactobacillus	60 million
Example XX	
Cephalexin	500 mgm
Lactobacillus	60 million
Example XXI	
Cephalexin	250 mgm
Bromhexine	4 mgm
Lactobacillus	60 million
Example XXII	
Cephalexin	250 mgm
Probenecid	250 mgm
Lactobacillus	60 million

Example XXIII		Example XXIV	
Cephalexin	500 mgm	Cefuroxime Axetil	125 mgm
Probenecid	500 mgm	Lactobacillus	60 million
Lactobacillus	60 million		
Example XXV		**Example XXVI**	
Cefuroxime Axetil	250 mgm	Cefuroxime Axetil	500 mgm
Lactobacillus	60 million	Lactobacillus	60 million
Example XXVII		**Example XXVIII**	
Cefixime	200 mgm	Cefixime	400 mgm
Lactobacillus	60 million	Lactobacillus	60 million

In above examples anti-infective agents can be used for any therapeutic purpose which in a therapeutic dosage causes significant adverse effects which can be presented by using an organism. The organism can be any which prevents or minimises adverse reactions of anti-infective agents when taken at same time. For prevention of diarrhoea, pseudomembranous colitis it can be biofidobacterium, sacchormyces streptococcus thermophilus, enterococcus etc. instead of lactobacillus in above examples in their appropriate dosages.

2. Following are examples of providing barrier to organisms for different dosage forms. However, it is not intended that the scope of this invention be limited by these examples.

Example I

Capsules :

i) Organisms can be lumped together and formulated into a tablet. The tablet coated with a barrier film. The film protected organisms are introduced into the capsule independently. Anti-infective agent is put in the capsule containing organisms protected by a barrier film. It can be vice versa.

ii) Organisms can be granulated. Granules containing organisms are coated barrier film. Barrier film coated granules are mixed with anti-infective agent before filling them into capsules.

Example II

Tablets :

i) Layered tablets :

Organisms are coated and compressed into a layer of tablet. The other layer(s) of tablet contains anti-infective agent.

ii) Tablet containing mixture :

Granules of organisms are coated with barrier film and mixed with granulated material of anti-infective agents and compressed into a tablet.

iii) Coated Tablets :

Anti-infective agents are formulated into compressed tablet. They are coated. During coating stage organisms are introduced in the coating. The coating should be capable of protecting organisms from anti-infective agents. It can be vice versa i.e. anti-infective agent is included in coating.

iv)

Tablet with a hole is produced containing anti-infective agent. The hole of the tablet is filled with organisms. The tablet so obtained may be coated for final finishing.

Coating/barrier protection is not so much necessary as it is in a capsule form as long as moisture content is controlled and physical separation is maintained in a same tablet. Formulated tablet can be dispersible tablet or simple tablet.

Example III

Liquid formulations :

i) The organisms are coated with barrier film mixed with other ingredients (dry form) of formulation including anti-infective agent. The product is reconstituted before use by addition of adequate amount of liquid.

ii) The organisms are coated with barrier film and suspended in a liquid containing anti-infective agents or vice versa. The barrier film is stable in liquid formulation but disintegrates in body due to alteration in surrounding, e.g. pH

3. Following are examples of coating agents which can be used in making stable fixed dose pharmaceutical composition containing anti-infective agent(s) and micro organism. However, it is not intended that the scope of this invention be limited by these examples.

	Chemical Name	Trade Name
1.	Cellulose acetate phthalate	Aquateric CAP Cellacefate
2.	Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1	Eudragit E 100 Eudragit E 12.5

3.	Poly(ethyl acrylate, methyl methacrylate) 2:1	Eudragit NE 30D (formerly Eudragit 30D)
4.	Poly(methacrylic acid, methyl methacrylate) 1:1 Eudragit L 12.5	Eudragit L 100 Eudragit L 12.5 P
5.	Poly(methacrylic acid, ethyl acrylate) 1:1	Eudragit L 30 D-55 Eudragit L 100-55
6.	Poly(methacrylic acid, methyl methacrylate) 1;2	Eudragit S 100 Eudragit S 12.5 Eudragit S 12.5 P
7.	Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2	Eudragit RL 100 Eudragit RL PO Eudragit RL 30 D Eudragit RL 12.5
8.	Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1	Eudragit RS 100 Eudragit RS PO Eudragit RS 30 D Eudragit RS 12.5
9.	Hydrogenated Castor Oil	Castrowax Castrowax MP 70 Castrowax MP 80 Opalwax Simulsol
10.	Cetyl Alcohol	Crodacol C70 Crodacol C90 Crodacol C95
11.	Diethyl Phthalate	Kodaflex DEP Palatinol A
12.	Ethyl cellulose	Aquacoat Ethocel Surelease
13.	Hydroxypropyl Cellulose	Klucel Methocel Nisso HPC
14.	Hydroxypropyl Methylcellulose Phthalate	--
15.	Zein	--

4. Following are examples of methods of preparing fixed dose stable pharmaceutical composition. However, it is not intended that the scope of this invention be limited by these examples.

Example I - Double layered Tablet

A stable fixed dose combination layered tablet is prepared using the following components of which the active ingredients are anti-infective agent(s) and micro organisms. The remaining components are physiologically acceptable excipients. One of the active ingredients is coated in a coating pan by the coating process known to those skilled in the art. Excipients are also used along with one of the active ingredients (granules) during tablet making for lubrication as required for the purpose. Granules of separate active ingredients are first prepared by process known to those skilled in the art. The separate sets of granules are then compressed on double rotary tablet compression machine having a laying facility at a temperature below 25°C and relative humidity not more than 50% by processes known to those skilled in the art and the tablets are transferred to a coating pan for film coating to be given by using film coating process known to those skilled in the art.

i) The relative proportion of anti infective agents and excipients to prepare coating suspension and coating anti-infective agents before granulation :

Ingredients	Parts by weight
Anti infective agent	77.54%
Ethyl cellulose	2.70%
Isopropyl alcohol	7.42%
Dichloromethane	12.34%

ii) The relative proportion of anti-infective agents and excipients to prepare granules :

Ingredients	Parts by weight
Anti-infective agent	64.08%
Microcrystalline cellulose	26.45%
Starch	9.00%
Colour Sunset Yellow Lake	0.45%
Purified water	0.02%

iii) The relative proportion of excipients to be added to granules containing anti-infective agents as lubricants :

Ingredients	Parts by weight
Sodium chloride	31.91%
Polyplasdone XL	14.89%
Microcrystalline cellulose	21.28%
Saccharine sodium	10.64%
Flavour orange	10.64%
Magnesium stearate	5.32%
Purified Talc	5.32%

iv) The relative proportion of micro organisms and excipients to prepare granules:

Ingredients	Parts by weight
Micro organisms	18.18%
Starch	18.18%
Microcrystalline cellulose	56.67%
Magnesium stearate	0.91%
Polyplasdone XL	3.03%
Sodium chloride	3.03%

The fixed dose layered tablet composition which are prepared through making use of above described process contain the above active ingredients anti-infective agents and viable organisms in their respective therapeutic concentration. The composition provide pharmacological effects which are complementary to the effects produced by (Prior art) each individual ingredient and are stable for a period of atleast 3 - 36 months at ambient room temperature.

Example II - Capsules

A stable fixed dose combination capsules are prepared using following components of which the active ingredients are anti-infective agents and micro organisms. The remaining components are physiologically acceptable excipients. Granules of one of the active ingredients (e.g. micro organisms) are first prepared by process known to those skilled in the art. The granules so formed are compressed into a tablet by tablet compression machine heaving a laying facility at a temperature below 25°C and relative humidity not more than 50% by process known to those skilled in the art. Tablets are transferred to a coating pan for coating to be given by coating process known to those skilled in the art.

The remaining active ingredient is mixed with excipients and filled into gelatin capsules by process known to those skilled into the art. Before sealing of capsules the coated tablet containing active ingredients are introduced into capsule by processes known to those skilled in the art.

i) The relative proportion of anti-infective agent and excipients for filling in capsule :

Ingredients	Parts by weight
Anti-infective agent	91.94%
Pregelatinised starch	6.24%
Magnesium stearate	1.44%
Sodium lauryl sulfate	0.38%

ii) The relative proportion of micro organism and excipients to prepare granules as follows :

Ingredients	Parts by weight
Micro organism	42.86%
Micro crystalline cellulose	53.93%
Magnesium stearate	1.07%
Colloidal silicone dioxide	0.71%
Cross carmellose sodium	1.43%

iii) The relative proportion of excipients to prepare coating suspension for coating of a tablet containing micro organisms to be kept into a capsule :

Ingredients	Parts by weight
Hydroxy propyl methyl cellulose pthalate	4.37%
Titanium dioxide	0.96%
Purified Talc	0.19%
Polyethelene glycol	0.99%
Isopropyl alcohol	34.95%
Dichloromethane	58.54%

The fixed dose capsule composition which are prepared through making use of above described process contain the above active ingredients, anti infective agents and viable organisms in their respective therapeutic concentrations. The composition provide pharmacological effect which are complementary to the effects produced by (prior art) each individual ingredient and are stable for at least 3 - 36 months at ambient room temperature.

Example III - Liquid Suspension

A stable fixed dose combination liquid tablet is prepared using the following components of which the active ingredients are anti-infective agent(s) and micro organisms. One of the active ingredients is granulated after suspending it in a coating suspension to provide granules of 100 micron or less in size by processes known to those skilled in art. Granules so prepared are suspended into a liquid formulation by processes known to those skilled in the art. The other active ingredient is introduced into the suspension by the process known to those skilled in the art in such a way that final concentration of micro organisms is 20% of anti infective agent(s).

The relative proportion of anti-infective agent and excipients to prepare coated granules :

Ingredients	Parts by weight
Anti infective agent	56.82%
Cellulose acetate pthalate	22.73%
Isopropyl alcohol	6.82%
Dichloromethane	13.63%

The fixed dose liquid suspension composition which is prepared through making use of above described process contain the above active ingredients. anti infective agents and viable organisms in their respective therapeutic concentrations. The composition provide pharmacological effect which are complementary to the effects produced by (prior art) each individual ingredient and are stable for at least 3 - 36 months at ambient room temperature.

Example IV - Dry Powder composition to make liquid composition after reconstitution.

A stable fixed dose combination dry powder for reconstituting liquid formulation before use is prepared using the following components of which the active ingredients are acceptable excipients.

One of the active ingredients is granulated after suspending it in a coating suspension by process known to those skilled in the art. The granules so prepared are dried and mixed with dry powder containing another active ingredient by processes known to those skilled in the art in such a way that micro organisms are 20% of anti infective agent(s) by weight.

The relative proportion of anti infective agents and the excipients to prepare coated granules is as follows :

Ingredients	Parts by weight
Anti infective agent(s)	50%
Hydroxy propyl methyl cellulose K-15 M (1,00,000 cps)	45%
Purified water	5%

The fixed dose dry powder composition which are prepared through making use of above described process contain the above active ingredients, anti infective agents and viable organisms in their respective therapeutic concentrations. The composition provide pharmacological effect which are complementary to the effects produced by (prior art) each individual ingredient and are stable for at least 3 - 36 months at ambient room temperature.

Above composition when reconstituted by adding liquid prior to use remains stable at ambient room temperature for 3 to 7 days.

5. Following are examples of therapeutic dosage of various anti-infective agents and micro organisms. However, it is not intended that the scope of this invention be limited by these examples.

A. Anti-infective agents

Anti infective agents can be penicillins e.g. ampicillin, amoxycillin, cloxacillin, cephalosporins e.g. cephalexin, cefadroxyl, cefuroxime axetil, cefixime, beta lactamase inhibition like clauvanic acid - macrolide like erythromycin as single ingredient or combination thereof.

i. Solid dosage forms like capsules or tablet contains anti infective agents equivalent to 125, 250 or 500 mgm of active component

ii. Liquid dosage forms usually contains anti infective agents equivalent to 125 mgm of active component in 5 ml.

B. Micro organism which can be used for therapeutic purposes and the dosage are as under :

1.	Lactobacillus Aciophillus	10 to 100 million
2.	Lactobacillus Spores	30 - 60 x 10^6
3.	Lactobacillus Lactis	10 - 500 million
4.	Streptococcus thermophilus	10 million
5.	Streptococcus lactis	10 million
6.	Saccromyces cerevisea	10 million
7.	Lactobacilli GG	10^{10} units

CLAIMS

We claim :

1. A process to provide a stable fixed dose oral pharmaceuticals composition, composed of anti-infective agent(s) and micro organisms as active ingredients with their different respective sets of properties, which when taken together as in this invention in a single composition such as a capsule/tablet/liquid preparation made according to a conventional process, result in a composition producing a set of effects complementary to each other, and remaining stable over a period of 3 - 36 months.

2. A process as claimed in claim 1 to provide a stable pharmaceutical composition consisting essentially of a mixture of i) therapeutic concentration of anti-infective agent and ii) therapeutic concentration of micro organisms, admixed with physiological acceptable excipients selected in nature and amount to provide a solid/liquid oral dosage composition such as a capsule/tablet/liquid preparations with effects complementary to those provided by each separate active ingredient and which is stable for at least 36 months at ambient temperature.

3. A process as claimed in claim 1 & 2 to make a stable pharmaceutical composition wherein anti-infective agents are selected from various groups of anti-infective agents e.g. Ampicillin, Amoxycillin, Cloxacillin from Penicillins, Clavulanic acid, Sultamicin from Beta lactamase inhibitors, Cefuroxime axetil, Cefadroxyl, Cephalexin from cepahlosporins, Erythromycin from macrolides, Ciprofloxacin from 8-aminoquinolines alone or in combination and organisms are selected from Lactobacillus aciophillus, Lactobacillus spores, Lactobacillus lactis, Streptococcus thermophilus, Streptococcus lactis, Saccromyces cerevisea, Lactobacilli GG and/or in combination thereof.

4. A process as claimed in claims 1 - 3 to provide a stable pharmaceutical composition wherein the ratio of Anti-infective agent to organism is in the range of 2:1 to 25:1 and preferably in the range of 5:1.

5. A process as claimed in claims 1 - 4 which process comprises admixing separately anti-infective agent and organism with physiologically acceptable excipients to provide granules, of which at least one is coated, said granules being subsequently compressed into a layered tablet using a double rotary compression under strict environmental conditions of temperature below 25°C and relative humidity not more than 50%.

6. A process as claimed in claims 1 - 5 one of the active ingredients comprising the provision of the coated anti-infective agent of about 77.54% is coated by suspending coating in a suspension containing about 2.7% of ethyl cellulose dissolved in about 7.42% of isopropyl alcohol and about 12.34% of dichlormethane.

7. A process as claimed in claims 1 - 5 comprising the provision of granules of coated anti infective agents as claimed in claim 6 admixed with physiologically acceptable excipient by using a mixture of about 64.08% of anti infective agent about 26.45% of microcrystalline cellulose about 9.0% of starch, about 0.45% of colour sunset yellow lake of about 0.02% of purified water by wight of said mixture, said granules being subsequently compressed with granules of micro organisms into a layered tablet.

8. A process as claimed in claims 1 - 5 comprising the provision of granules of organism admixed with physiologically acceptable salts by using a mixture of about 18.18% of micro organisms, about 18.18% of starch, about 56.67% of microcrystalline cellulose, about 91% of magnesium stearate, about 3.03% of polyplasdone XL and 3.03% of sodium chloride by weight of the mixture, said granules being subsequently compressed with the coated granules of anti-infective agent into a layered tablet.

9. A process as claimed in claim 1 - 4 wherein one of the active ingredients is compressed into a tablet and coated, said coated tablet is put into a capsule containing another active ingredient.

10. A process as claimed in claim 1 - 4 and 9 comprising the provision of a tablet micro organism admixed with physiologically acceptable excipients by using a mixture of about 42.86% of micro organisms, about 53.93% of microcrystalline cellulose, about 1.07% of magnesium stearate, about 10.71% of colloidal silicone dioxide, about 1.43% of cross carmellose sodium by weight of said mixture.

11. A process as claimed in claim 1 - 4 and 9 comprising the provision of coating of the tablet is carried out by using a coating suspension comprising about 4.31% of hydroxy propyl methyl cellulose pthalate, about 0.96% of Titanium dioxide, about 0.19% of purified talk, about 0.91% of polyethelene glycol, about 4.95% of isopropyl alcohol, about 58.54% dichloro methane by weight of suspension.

12. A process as claimed in claim 1 - 4 and 9 comprising the provision anti-infective agents admixed with physiologically acceptable excipients by using a mixture of about 91.94% of anti-infective agent, about 6.24% of pregelatinised starch, about 1.44% of magnesium stearate, about 0.38% of sodium lauryl sulfate by weight of said mixture which is subsequently filled into capsules.

13. A process as claimed in claim 1 - 4 wherein one of the active ingredients is coated and suspended into a solution containing another active ingredient.

14. A process as claimed in claim 1 - 4 and claim 13 comprising of coating of anti-infective agent in which coating of about 56.82% of anti-infective agent is carried out by using a coating suspension comprising about 22.73% of cellulose acetate pthalate, about 6.82% of isopropyl alcohol, about 13.63% of dichloromethane by weight, said coated anti-infective agent is suspended in liquid.

15. A process as claimed in claim 1 - 4 and claim 14 comprising the provision of coated anti-infective agent in which coating of about 50% of anti-infective agent is carried out by using a coating suspension comprising about 45% of hydroxy propyl methyl cellulose K-15M (1,00,000 cps), about 5% of purified water by weight of said mixture.

16. A process as claimed in claim 1 - 4 wherein liquid preparation having shorter self life has to be dispensed in dry form, said dry form comprising the said two active ingredients wherein one of them is coated and kept in such a way so that when reconstituted it forms a suspension which is stable for 3 to 7 days at ambient temperature.

17. A process for preparation of a stable fixed dose pharmaceutical composition of anti-infective agent/agents and micro organism as active ingredients as claimed in claim 1 and subsequently herein described in examples 1 to 5 in the accompanying complete specification.

INTERNATIONAL SEARCH REPORT

Inter nal application No.
PCT/IB 98/00445

A. CLASSIFICATION OF SUBJECT MATTER

IPC^6: A 61 K 35/74 // (A 61 K 35/74; C 12 R 1:225,1:46,1:865)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC^6: A 61 K 35/74

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 306 465 A1 (LEJUS MEDICAL AKTIEBOLAG) 08 March 1989 (08.03.89), claims 1,3.	1-3
A	Patent Abstracts of Japan, Vol.13, No.286, 1989, JP 1-083025 A (FUJIO HAYASHI) 29 June 1989 (29.06.89), abstract.	1-3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1998 (16.12.98)	13 January 1999 (13.01.99)
Name and mailing address of the ISA/ Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Wolf Telephone No. 1/53424/436

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intc onal application No.
PCT/IB 98/00445

In Recherchenbericht angeführtes Patentdokument / Patent document cited in search report / Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung / Publication date / Date de publication	Mitglied(er) der Patentfamilie / Patent family member(s) / Membre(s) de la famille de brevets	Datum der Veröffentlichung / Publication date / Date de publication
EP A1 306465	08-03-89	AT E 78424	15-08-92
		DE D0 3872991	27-08-92
		DE T2 3872991	14-01-93
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